B1 Asp Gly Asn Ser Thr Arg Ser Pro Glu Thr Asn Gly Leu Leu Cys Gly Asp Pro Glu Glu Asn Cys Ala Ala Thr Thr Thr Gln Ser Lys Arg Lys Gly His Phe Ser Arg Cys Pro Lys (SEQ ID NO: 57)

Please replace the paragraph on page 15, lines 4-6, with the following paragraph:

B2 Gln Tyr Lys His Tyr Cys Ile Lys Gly Arg Cys Arg Phe Val Val Ala Glu Gln Thr Pro Ser Cys Val Cys Asp Glu Gly Tyr Ile Gly Ala Arg Cys Glu Arg Val (SEQ ID NO: 58)

Please replace the paragraph on page 15, lines 19-21, with the following paragraph:

B3 Asp Gly Asn Ser Thr Arg Ser Pro Glu Thr Asn Gly Leu Leu Cys Gly Asp Pro Glu Glu Asn Cys Ala Ala Thr Thr Thr Gln Ser Lys Arg Lys Gly His Phe Ser Arg (SEQ ID NO: 59)

Please replace the paragraph on page 16, lines 1-3, with the following paragraph:

B4 Cys Pro Lys Gln Tyr Lys His Tyr Cys Ile Lys Gly Arg Cys Arg Phe Val Val Ala Glu Gln Thr Pro Ser Cys Val Cys Asp Glu Gly Tyr Ile Gly Ala Arg Cys Glu Arg Val (SEQ ID NO: 60)

Please replace the paragraph on page 16, lines 17-22, with the following paragraph:

B5 Gly Asn Ser Thr Arg Ser Pro Glu Thr Asn Gly Leu Leu Cys Gly Asp Pro Glu Glu Asn Cys Ala Ala Thr Thr Thr Gln Ser Lys Arg Lys Gly His Phe Ser Arg Cys Pro Lys Gln Tyr Lys His Tyr Cys Ile Lys Gly Arg Cys Arg Phe Val Val Ala Glu Gln Thr Pro Ser Cys Val Cys Asp Glu Gly Tyr Ile Gly Ala Arg Cys Glu Arg Val (SEQ ID NO: 61)

Please replace the paragraph on page 17, lines 8-10, with the following paragraph:

B6 Asp Gly Asn Ser Thr Arg Ser Pro Glu Thr Asn Gly Leu Leu Cys Gly Asp Pro Glu Glu Asn Cys Ala (SEQ ID NO: 62)

Please replace the paragraph on page 17, lines 14-17, with the following paragraph:

B7

Ala Thr Thr Thr Gln Ser Lys Arg Lys Gly His Phe Ser Arg Cys Pro Lys Gln Tyr Lys His Tyr Cys Ile Lys Gly Arg Cys Arg Phe Val Val Ala Glu Gln Thr Pro Ser Cys Val Cys Asp Glu Gly Tyr Ile Gly Ala Arg Cys Glu Arg Val (SEQ ID NO: 63)

Please replace the paragraph on page 24, lines 23-26, with the following paragraph:

B8

Asp Gly Asn Ser Thr Arg Ser Pro Glu Thr Asn Gly Leu Leu Cys Gly Asp Pro Glu Glu Asn Cys Ala Ala Thr Thr Thr Gln Ser Lys (SEQ ID NO: 64)

On page 61, after line 19 and before the paragraph beginning at line 20, please insert the following paragraphs:

B9

SEQ ID NO: 57

the 1st to 40th amino acid sequence from N-terminal of betacellulin

SEQ ID NO: 58

the 41st to 76th amino acid sequence from N-terminal of betacellulin

SEQ ID NO: 59

the 1st to 37th amino acid sequence from N-terminal of betacellulin

SEQ ID NO: 60

the 38th to 76th amino acid sequence from N-terminal of betacellulin

SEQ ID NO: 61

the 2nd to 76th amino acid sequence from N-terminal of betacellulin

SEQ ID NO: 62

the 1st to 23rd amino acid sequence from N-terminal of betacellulin

SEQ ID NO: 63

the 24th to 76th amino acid sequence from N-terminal of betacellulin

SEQ ID NO: 64

the 1st to 30th amino acid sequence from N-terminal of betacellulin

Please replace the paragraph on page 64, lines 1-17, with the following paragraph:

The 77 residue (lacking three C terminal residues) betacellulin structural gene was amplified by PCR from the pB041 betacellulin expression plasmid (Seno et al, *Growth Factors*, 13:181 (1996)) using a primer 1 (5'-CATATGGATGGGAATTCCACCAGAAGTCCTG; SEQ ID NO: 29) having an NdeI cleavage site and start codon adjacent upstream of the structural gene and a primer 2 (5'-GGATCCCTAGTCAACTCTCTCACACCTTGCTCC; SEQ ID NO: 30) having a stop codon and BamHI cleavage site after the aspartic acid at 77. The gene thus amplified by PCR was ligated to the pCR2.1 vector using a TA original cloning kit (by Invitrogen) to prepare pCR2.1/BTC77. This was introduced to E. coli JM109, and transformants were selected using ampicillin resistance and β-galactosidase activity as indicators. Transformants having pCR2.1/BTC77 were cultured, and pCR2.1/BTC77 was prepared using a QIAprep8 Miniprep kit (by Qiagen).

Please replace the paragraph on page 68, lines 16 to page 69, line 4, with the following paragraph:

The 76 residue (lacking four C terminal residues) betacellulin structural gene was amplified by PCR from the pTCII/BTC77 constructed in Example 1 using primer 1 (5'-CATATGGATGGGAATTCCACCAGAAGTCCTG; SEQ ID NO: 29) having an NdeI cleavage site and start codon adjacent upstream of the structural gene and a primer 2 (5'-GGATCCCTAAACTCTCTCACACCTTGCTCCAATG; SEQ ID NO: 30) having a stop codon and BamHI cleavage site after the valine at 76. The gene thus amplified by PCR

was ligated to the pCR2.1 vector using a TA original cloning kit (by Invitrogen) to prepare pCR2.1/BTC76. This was introduced to E. coli JM109, and transformants were selected using ampicillin resistance and β-galactosidase activity as indicators. Transformants having pCR2.1/BTC76 were cultured, and pCR2.1/BTC76 was prepared using a QIAprep8 Miniprep kit (by Qiagen).

Please replace the paragraph on page 81, beginning at line 14 to page 82, line 12, with the following paragraph:

Genomic DNA was prepared in the conventional manner from rat tail. The 0.75 kb insulin promoter region was amplified by PCR with a primer RI-1 (5'-AGAGTCAAGGATCCCCCAACCACT-3'; SEQ ID NO: 31) and a primer RI-3 (5'-AGCTGGTCACTTAGGGCTGGGG-3'; SEQ ID NO: 32) based on the base sequence of the well known rat insulin II gene promoter (GenBank: Accession No. J00748) using the genomic DNA as template. PCR was also carried out using primers RI-1Cla (5'-GAATCGATAGAGTCAAGGATCCCCCA-3'; SEQ ID NO: 33) and RI-3Xho (5'-GACTCGAGCTGGTCACTTAGGG-3'; SEQ ID NO: 34) using the PCR product as template. The amplified 0.75 kb DNA fragments were isolated, and the pTB1881 plasmid obtained upon insertion into the pT7 Blue vector (Novagen 69820-1) was used to sequence the base sequence of the cloned fragments, confirming that they were the rat insulin promoter. The pTB1881 plasmid was digested with XhoI-ClaI, giving 0.73 kb DNA fragments (rat insulin promoter). The pTB1330 plasmid for the expression of 2.0 kb cDNA (J. Berger et al., *Gene,* 66, 1 (1988)) encoding human placenta alkaline phosphatase (PLAP) was digested with XhoI-HindIII. The resulting 2.7 kb DNA fragments (PLAP cDNA, containing an SV40-derived splicing site and polyA addition site, pBR322-derived ori, and ampicillin resistance gene) were isolated, and the aforementioned rat insulin promoter region 0.73 kb XhoI-CalI fragment was ligated by T4 DNA ligase reaction, giving the plasmid pTB1898.

Pl as replace the paragraph on pag 85, line 6-23, with th f llowing paragraph:

The 2-76 residue (lacking one N terminal residue and three C terminal residues) betacellulin structural gene was amplified by PCR from the 76-residue (lacking three C terminal residues) betacellulin expression plasmid pTCIIBTC76 (Example 4) using a primer 3 (5'-CAGCATATGGGGAATTCCACCAGAAGTCCT; SEQ ID NO: 39) having an NdeI cleavage site and start codon adjacent upstream of the glycine at 2 and a primer 4 (5'-GGATCCCTAAACTCTCTCACACCTTGCTCCAATG; SEQ ID NO: 40) having a stop codon and BamHI cleavage site after the valine of the C terminal. The gene thus amplified by PCR was ligated to the pCR2.1 vector using a TA original cloning kit (by Invitrogen) to prepare pCR2.1BTC2-76. This was introduced to E. coli JM109, and transformants were selected using ampicillin resistance as an indicator. Transformants having pCR2.1BTC2-76 were cultured, and pCR2.1BTC2-76 was prepared using a QIAprep8 Miniprep kit (by Qiagen).

Please replace the paragraph beginning on page 89, line 11 to page 90, line 2, with the following paragraph:

The 24-76 residue (lacking 23 N terminal residues and three C terminal residues) betacellulin structural gene was amplified by PCR from the 76-residue (lacking three C terminal residues) betacellulin expression plasmid pTCIIBTC76 prepared in Example 4 using a primer 5 (5'-CAGCATATGGCTACCACCACACAATCAAAG; SEQ ID NO: 41) having an NdeI cleavage site and start codon adjacent upstream of the alanine at 24 and a primer 4 (5'-GGATCCCTAAACTCTCTCACACCTTGCTCCAATG; SEQ ID NO: 40) having a stop codon and BamHI cleavage site after the valine of the C terminal. The gene thus amplified by PCR was ligated to the pCR2.1 vector using a TA original cloning kit (by Invitrogen) to prepare pCR2.1BTC24-76. This was introduced to E. coli JM109, and transformants were selected using ampicillin resistance as an indicator. Transformants having pCR2.1BTC24-76 were cultured, and pCR2.1BTC24-76 was prepared using a QIAprep8 Miniprep kit (by Qiagen).

On page 101, please replace the paragraphs beginning line 7 after the Table and ending at page 102, line 5 with the following paragraphs:

PCR was carried out with pTB1976 as template using (1) a 5' side primer PET-1 (5'-GAAATAATTTTGTTTAACTTTAAGAAGGAG-3'; SEQ ID NO: 52) and a 3' side primer BTC-1 (5'-AGGAGGGCGTCGAGGGGTTCTGCTCGGCCA-3'; SEQ ID NO: 53) and (2) 5' side primer BTC-2 (5'-TGGCCGAGCAGAACCCCTCGACGCCCTCCT-3'; SEQ ID NO: 54) and a 3' side primer BTC-3 (5'-TCTATGCGCACCCGTTCTCGGAGCACTGTC-3'; SEQ ID NO: 55).

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A mixture of the PCR products of (1) and (2) was used as template for PCR using a 5' side primer BT-95h (SEQ ID NO: 50) and a 3' side primer BT-94h (SEQ ID NO: 51), giving DNA fragments encoding mutein A with 3 amino acids (Asn, Pro, Ser) of the Her sequence inserted between the Cys3-Cys4 of hBTC50. The DNA fragment was digested with NdeI and BamHI, and then inserted into the NdeI-BamHI position of pET-3c to prepare pTB1985.

Please replace the paragraph on page 102, line 14-21, with the following paragraph:

pTB1976 was used as template in PCR using a 5' side primer BTC-7 (5'-TATACATATGAACAGCGACTCTGAGTGCCCCAAGC-3'; SEQ ID NO: 56) and the 3' side primer BT-94h (SEQ ID NO: 51), giving DNA fragments encoding mutein B in which seven N terminal residues of hBTC50 were substituted with five corresponding EGF residues. The DNA fragment was digested with NdeI and BamHI, and then incorporated into the NdeI-BamHI position of pET-3c to prepare pTB1987.

B16

Please replace the paragraph on page 109, line 4 from the bottom to page 110, line 22, with the following paragraph:

Genomic DNA was prepared in the conventional manner from rat tail. The 0.75 kb insulin promoter region was amplified by PCR with a primer RI-1 (5'-AGAGTCAAGGATCCCCCAACCACT-3'; SEQ ID NO: 31) and a primer RI-3 (5'-AGCTGGTCACTTAGGGCTGGGG-3'; SEQ ID NO: 32) based on the base sequence of the well known rat insulin II gene promoter (GenBank: Accession No. J00748) using the genomic DNA as template. PCR was also carried out using primers RI-1Cla (5'-GAATCGATAGAGTCAAGGATCCCCCA-3'; SEQ ID NO: 33) and RI-3Xho

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(5'-GACTCGAGCTGGTCACTTAGGG-3'; SEQ ID NO: 34) using the PCR product as template. The amplified 0.75 kb DNA fragments were isolated, and the pTB1881 plasmid obtained upon insertion into the pT7 Blue vector (Novagen 69820-1) was used to sequence the base sequence of the cloned fragments, confirming that they were the rat insulin II promoter. The pTB1881 plasmid was digested with XhoI-ClaI, giving 0.73 kb DNA fragments (rat insulin promoter). The pTB1330 plasmid for the expression of 2.0 kb cDNA (J. Berger et al., *Gene,* 66, 1 (1988)) encoding human placenta alkaline phosphatase (PLAP) was digested with XhoI-HindIII. The resulting 2.7 kb DNA fragments (PLAP cDNA, containing an SV40-derived splicing site and polyA addition site, pBR322-derived ori, and ampicillin resistance gene) were isolated, and the aforementioned rat insulin promoter region 0.73 kb XhoI-ClaI fragment was ligated by T4 DNA ligase reaction, giving the plasmid pTB1898.

Please replace the paragraph on page 113, line 6-21, with the following paragraph:

The pTB1516 plasmid incorporating the cDNA of 80-residue hBTC (Japanese Unexamined Patent Application (Kokai) H6-87894; Accession No. FERM BP-3836, Accession No. IFO 15282) was used as template in PCR using the BT-95h primer (5'-AGCATATGCGGAAAGGCCACTTCTCTAGGT-3'; SEQ ID NO: 50) and the BT-94h primer (5'-CTGGATCCTAGTAAAACAAGTCAACTCTCT-3'; SEQ ID NO: 51). PCR products with a translation start codon and NdeI site in the 5' terminal of the C terminal 50-residue type hBTC, and a stop codon and a BamHI site inserted at the 3' terminal, were digested with NdeI and BamHI, and were inserted using the DNA Ligation Kit Ver. 2 (Takara) to the NdeI-BamHI site of the pET-3c expression plasmid (Novagen) having the Φ10 promoter of the T7 phage, so as to prepare the pTB1976 plasmid for the expression of hBTC50. The base sequence of the inserted cDNA was confirmed by an ABI DNA sequencer (ABI377 DNA Sequencer).